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An das
Deutsche Patent-
und Markenamt

80297 München

Munich, July 15, 2003

Unsere Akte:
Our Ref.: M/44090

Betreff: **German Utility Model DE 201 16 428.0**
Re: **Cancellation request by CIMEX DEVELOPMENT AG**
LÖ I 13/03

Translation of the response as filed to the cancellation request by Cimex

The following observations are made on the cancellation request by CIMEX DEVELOPMENT AG:

I. REQUESTS

It is requested that

1. the cancellation request be rejected, alternatively the cancellation request be rejected and the utility model be maintained on the basis of the appended claims according to auxiliary request 1 and further alternatively on the basis of the appended claims according to the auxiliary request 2.

2. the applicant be ordered to bear the costs of the cancellation proceedings.

II. SUBJECT-MATTER OF THE UTILITY MODEL

1. According to the main request the subject-matter of the utility model is as

registered.

2. Auxiliary Request 1

Claim 1 of the first auxiliary request relates to a

> pharmaceutical composition comprising an effective amount of amlodipine maleate and at least one pharmaceutically acceptable excipient, wherein the composition has a pH within the range of 5.5 to 7.0 and is not a solution.

The claim is based on the registered claim 1 and it was expressed that the composition is not in the form of a solution.

The subject-matter of new claim 3 is disclosed in the 3rd and 4th paragraph on page 7 of the utility model.

The subject-matter of new claim 8 is disclosed in the second paragraph on page 9 of the utility model.

New claims 2, 4 to 7 and 9 to 13 correspond to registered claims 2, 4 to 6 and 8 to 13.

New claims 14 and 15 are based on registered claims 20 and 19 and have been worded as *product-by-process* claims.

2. Auxiliary request 2

The subject-matter of claim 1 according to the second auxiliary request is a

> solid pharmaceutical composition comprising an effective amount of amlodipine maleate and at least one pharmaceutically acceptable excipient having a pH effect, wherein the composition has a pH within the range from 5.5 to 7.0.

The claim refers to a solid composition. This is disclosed in registered claim 3. The definition of the excipient as having a pH effect is disclosed in the last paragraph on page 7 of the utility model.

New claims 2 to 4 and 6 to 12 are based on registered claims 2, 4 to 6 and 9 to 13, with registered claim 4 having been divided up and made the subject-matter of new claims 3 and 6.

The subject-matter of new claim 5 is disclosed in the 3rd paragraph on page 7 of the utility model. New claims 13 and 14 correspond to claim 14 and 15 in the auxiliary request 1, see above.

The subject-matter of the utility model is thus according to all requests a pharmaceutical composition with amlodipine maleate as active ingredient and having a pH in the range 5.5–7.0. In case of a solid composition, the stated pH is measured on a 20% slurry of the composition in water, see the paragraph connecting pages 4 and 5.

III. THE PROTECTABILITY OF THE UTILITY MODEL

The cancellation request is based on the following prior art:

D1: US 5,155,120
D2: WO 95/34299
D3: US 4,590,195
D4: US 4,879,303
D5: US 6,057,344.

The applicant asserts that the subject-matter of the utility model is not novel in relation to D1, D2 and D5. It is moreover said not to involve an inventive step in the light of D3 to D5.

A. MAIN REQUEST

1. Novelty

1.1 Concerning D1, the applicant asserts that this describes pharmaceutical compositions containing amlodipine maleate together with certain excipients specified in D1. However, it has not apparently escaped the applicant's notice that D1 does not describe pharmaceutical compositions with amlodipine maleate and having a pH in the range from 5.5 to 7.0. The applicant is therefore attempting, by referring to statements in the utility model specification, to show an agreement with the description in D1. In the first place, the applicant regards the excipients sodium citrate, calcium carbonate and dicalcium phosphate, which are listed in column 2,

lines 44 and 45, as pH-inert excipients. The use of pH-inert excipients does not, in contrast to the applicant's opinion, inevitably lead to a composition which has a pH in the range indicated in claim 1. This is because amlodipine maleate is acidic and has, for example, as saturated aqueous solution, a pH of about 4.8, see page 7, 3rd paragraph of the utility model. A combination with a pH-inert excipient may therefore very possibly have a pH outside the range under discussion here. In addition, said excipients are not pH-inert. An aqueous solution of sodium citrate and dicalcium phosphate generally has a pH in the alkaline range. This is evident for dicalcium phosphate from the first paragraph on page 8, lines 1 to 3, of the utility model. A slurry of calcium carbonate in water has a pH of 9. In addition, calcium carbonate may react with the acidic amlodipine maleate with the result that the pH is shifted even further into the alkaline region.

As already mentioned, D1 makes no statements at all about the pH of compositions containing amlodipine or a salt thereof together with a pharmaceutically acceptable excipient. Above all, it contains no statements about the pH of a composition containing amlodipine maleate. Hence, precisely the essential feature of the compositions of the invention is not disclosed in D1. In other words, the teaching about the pH of an amlodipine maleate-containing solid oral composition being controlled and adjusted to a value in the range from 5.5 to 7.0 is not present in D1. The subject-matter of the utility model is thus novel in relation to D1.

1.2 D2 is concerned with the constriction of the pupil which may occur during operations on the eye. A method for inhibiting intraoperative miosis or for producing intraoperative mydriasis is therefore described. This entails introducing an L-type calcium channel blocker into the intraocular chamber of a patient during an intraocular operation, see, for example, page 2, lines 26 to 29. The only L-type calcium channel blocker seriously contemplated is diltiazem. A pharmaceutical composition comprising an effective amount of amlodipine maleate and at least one pharmaceutically acceptable excipient wherein said composition has a pH within the range f 5.5 to 7.0 is, in contrast thereto, not disclosed in combination.

1.3 The applicant's argument in relation to D5 is similar to that for D1, the assertion being that, according to the statements in the specification of the utility model, a composition comprising amlodipine maleate and microcrystalline cellulose generally has a pH of about 6. Since such a composition is described in D5, the subject-matter of the utility model is said not to be novel.

As already stated in connection with D1, it is by no means the case that a composition of amlodipine maleate and microcrystalline cellulose or another pH-inert

excipient inevitably has a pH in the range from 5.5 to 7.0. The reason for this is that amlodipine maleate itself when dissolved in water results in a pH of about 4.8, i.e. the pH can be outside the range stated in claim 1 even in compositions containing amlodipine maleate and a pH-inert excipient.

D5 contains, like D1, no statements at all about the pH of the compositions containing (-)-amlodipine or a salt thereof, let alone about the pH of compositions containing amlodipine maleate. In other words, D5 does not disclose the teaching about the pH of a pharmaceutical composition containing amlodipine maleate and a pharmaceutically acceptable excipient being controlled and adjusted to a value in the range from 5.5 to 7.0, either. The subject-matter of claim 1 is therefore novel in relation to D5 too.

The applicant has not rightly disputed novelty in relation to D3 and D4 because this prior art has nothing to do with amlodipine or amlodipine maleate. It should thus be stated that the subject-matter of the utility model is novel in relation to the cited prior art.

2. The presence of an inventive step

2.1 It is stated in the introduction to the description of the utility model that amlodipine maleate was originally intended for the development and approval of a drug product. However, it emerged during the investigations necessary for approval that difficulties occur in the tableting and in relation to the stability of amlodipine maleate. Further development of amlodipine maleate was therefore abandoned and a switch was made to amlodipine besylate, see the paragraph connecting pages 2 and 3 of the specification of the utility model. Up to the present time, only amlodipine besylate is on the market, under the proprietary name NORVASC.

2.2 On this basis, the object of the present invention is to provide stable pharmaceutical compositions containing amlodipine maleate.

2.3 The proprietor of the utility model has now found that this object is achieved and the stability problems are overcome when the pH of the amlodipine maleate-containing compositions is controlled so that it is in the range from 5.5 to 7.0. The proprietor of the utility model has found that the tableting and stability problems are caused by amlodipine aspartate, a degradation product of amlodipine maleate. It has emerged that controlling the pH reduces or even prevents the formation of amlodipine aspartate and thus also the tableting and stability problems.

2.4 In the cited prior art relating to amlodipine maleate, the stability problem is not mentioned at all. Nor is there the slightest reference to controlling the pH of amlodipine maleate compositions or to adjusting it to a value in the range from 5.5 to 7.0. The prior art thus contains nothing which could have prompted the skilled person to achieve the abovementioned object by means of the claimed composition. It was therefore not obvious, but on the contrary surprising, that stable amlodipine maleate-containing compositions were obtained through controlling the pH. The results of the stability studies compiled in Example 5 confirm this emphatically. The results show that in compositions with a pH in the range from 5.5 to 7.0 the amlodipine aspartate content and the amlo-pyridine content has surprisingly increased only slightly even after storage at 40°C for three months. In contrast to this, with a comparative composition having a pH of 8.68 (Example 4), the amlodipine aspartate content after storage for only one month is considerably higher than for the compositions of the invention after three months, cf. the tables on pages 19 to 23.

In these circumstances, the subject-matter of claim 1 also involves an inventive step.

2.5 The applicant's statements cannot alter this assessment in any way. They are incorrect and are based on an inadmissible ex post facto analysis. Thus, D3 relates not to amlodipine maleate but to quite different 1,4-dihydropyridine compounds. In these compounds, the side chain of the 1,4-dihydropyridine no longer contains the free amino group. On the contrary, at least one hydrogen atom of the amino group is replaced by one of the radicals R^4 specified in line 55 in column 1. These radicals greatly alter the reactivity of the amino group, and it reduces its basic and nucleophilic properties. The compounds are therefore not very similar, as asserted by the applicant, but are compounds differing markedly from amlodipine maleate in their structure and their chemical properties. However, it is precisely the chemical properties which matter in this connection. This is because the stability problem associated with amlodipine maleate cannot occur with these compounds because the presence of the radical R^4 means that addition onto the double bond of maleic acid is impossible and amlodipine aspartate cannot be formed. An additional point is that D3 does not contain the slightest reference to controlling the pH of the compositions, let alone adjusting it to a value in the range from 5.5 to 7.0. The applicant's statements are therefore beside the point.

D4 in turn relates to amlodipine besylate. This is the salt of amlodipine with benzenesulfonic acid. A stability problem comparable to amlodipine maleate owing to addition of the free amino group of amlodipine onto the double bond of maleic acid cannot occur because the structure of benzenesulfonic acid is completely different. On the contrary, it is shown in D4 that amlodipine besylate is particularly stable, and

the maleate is unstable, see the table at the start of column 3. D4 therefore merely confirms the starting point of the present invention, namely that pharmaceutical compositions with amlodipine maleate display stability problems. In these circumstances, the skilled person has not the slightest reason to give any consideration at all to D4 in order to achieve the abovementioned object. Besides, D4 makes no suggestion about controlling the pH of an amlodipine maleate composition or adjusting it to a value in the range from 5.5 to 7.0.

D5 relates to an optical isomer of amlodipine. The salts thereof are only referred to in general form and only a list of possible salt-forming acids is given. No particular salt, let alone the maleate is specifically addressed. Further, the stability problem is not mentioned at all. Example 8 referred to by the applicant contains amlodipine free base and not a salt, let alone the maleate. A person skilled in the art therefore will not at all consider the teaching of D5 or example 8 in order to solve the above mentioned problem. As already mentioned above, it is an inadmissible ex post facto consideration to consider example 8 as relevant.

2.6 The subclaims are dependent claims which relate back directly or indirectly to claim 1. They are therefore maintained together with claim 1.

B. AUXILIARY REQUESTS

1. Novelty

The statements made above in connection with D1, D2 and D5 apply correspondingly for the auxiliary requests. The following supplemental remarks have to be made:

As mentioned above in connection with the main request, the applicant has referred to the excipients sodium citrate, calcium carbonate and dicalcium phosphate in relation to D1. These are excipients exerting an effect on the pH. However, said excipients give rise to a pH which is in the alkaline range. A composition with amlodipine maleate having a pH in the range from 5.5 to 7.0 is therefore not disclosed in D1. The subject-matter of the auxiliary requests is thus novel in relation to D1.

D2 refers, as mentioned above, to a method for inhibiting intraoperative miosis or for producing intraoperative mydriasis. This entails introducing an L-type calcium channel blocker into the intraocular chamber of a patient. It is entirely clear that in

operations on the eye a pharmaceutical composition must be used in the form of a solution. D2 also considers only such solutions. This is evident from the entire contents of D2, being most clearly expressed on page 9, lines 16 and 17, and on page 10, lines 2 to 4. D2 thus describes neither a pharmaceutical composition which is in a form other than a solution, to say nothing of a solid amlodipine-containing composition. The subject-matter of the auxiliary requests is thus novel also in relation to D2.

D5 in turn does not describe any compositions containing an excipient exerting an effect on the pH. In these circumstances, the subject-matter of the auxiliary requests is novel in relation to D5, too.

2. Presence of an inventive step

The statements made above in connection with the main request apply correspondingly here, i.e. the subject-matter of the auxiliary requests also comprises an inventive step.

P. Riedl 259/mm

Enclosures:
Claims 1 to 15 according to the auxiliary request 1 (triplicate)
Claims 1 to 14 according to the auxiliary request 2 (triplicate)
1 copy of this letter including enclosures

English translation of the claims according to

Auxiliary Request 1

Claims

1. A pharmaceutical composition comprising an effective amount of amlodipine maleate and at least one pharmaceutically acceptable excipient wherein said composition has a pH within the range of 5.5 to 7.0 and is not a solution.

2. The composition according to claim 1, wherein said composition has a pH of about 6.0 to 7.0

3. The composition according to claims 1 or 2, wherein said excipient is a pH-inert excipient and/or an excipient having a pH effect.

4. The composition according to any of the preceding claims, wherein said excipient is a calcium phosphate or microcristalline cellulose.

5. The composition according to claim 4, wherein said composition comprises a calcium phosphate and microcristalline cellulose.

6. The composition according to claim 4 or 5, wherein the calcium phosphate is calcium hydrogen phosphate.

7. The composition according to any one of the preceding claims, wherein the excipient having a pH effect is an acidic excipient.

8. The composition according to any of the preceding claims in the form of a solid or a suspension.

9. The composition according to claim 8, wherein the composition is in the form of a tablet.

10. The composition according to claim 9, wherein the tablet further comprises an outer moisture and/or light barrier layer surrounding said tablet.

11. The composition according to claim 8, wherein said composition is in the form of a capsule.

12. The composition according to any of the preceding claims, wherein the amount of amlodipine maleate corresponds to 1.0 to 25 mg of amlodipine free base.

13. The composition according to claim 12, wherein said amount of amlodipine maleate corresponds to 1.25, 2.5, 5 or 10 mg of the amlodipine free base.

14. The composition according to any of the preceding claims, obtainable by using amlodipine maleate in the form of solid particles having an average particle size of at least 20 µm.

15. The composition according to claim 14, wherein the average particle size of the amlodipine maleate is at least 100 µm.

English translation of the claims according to

Auxiliary Request 2

Claims

1. Solid pharmaceutical composition comprising an effective amount of amlodipine maleate and at least one pharmaceutically acceptable excipient having a pH effect wherein said composition has a pH within the range of 5.5 to 7.0.

2. The composition according to claim 1, wherein said composition has a pH of about 6.0 to 7.0.

3. The composition according to claims 1 or 2, wherein the excipient having a pH effect is a calcium phosphate.

4. The composition according to claim 3, wherein the calcium phosphate is calcium hydrogen phosphate.

5. The composition according to any of the preceding claims, further comprising a pH-inert excipient.

6. The composition according to claim 5, wherein the pH-inert excipient is microcristalline cellulose.

7. The composition according to claim 6, wherein said composition comprises a calcium phosphate and microcristalline cellulose.

8. The composition according to any of the preceding claims, wherein the composition is in the form of a tablet.

9. The composition according to claim 8, wherein the tablet further comprises an outer moisture and/or light barrier layer surrounding said tablet.

10. The composition according to any of the preceding claims 1 to 7, wherein said composition is in the form of a capsule.

11. The composition according to any of the preceding claims, wherein the amount of amlodipine maleate corresponds to 1.0 to 25 mg of amlodipine free base.

12. The composition according to claim 11, wherein said amount of amlodipine maleate corresponds to 1.25, 2.5, 5 or 10 mg of the amlodipine free base.

13. The composition according to any of the preceding claims, obtainable by using amlodipine maleate in the form of solid particles having an average particle size of at least 20 µm.

14. The composition according to claim 13, wherein the average particle size of the amlodipine maleate is at least 100 µm.